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REVIEW ARTICLE

μ opioid receptor, social behaviour and autism spectrum disorder: reward matters

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The endogenous opioid system is well known to relieve pain and underpin the rewarding properties of most drugs of abuse. Among opioid receptors, the μ receptor mediates most of the analgesic and rewarding properties of opioids. Based on striking similarities between social distress, physical pain and opiate withdrawal, μ receptors have been proposed to play a critical role in modulating social behaviour in humans and animals. This review summarizes experimental data demonstrating such role and proposes a novel model, the μ opioid receptor balance model, to account for the contribution of μ receptors to the subtle regulation of social behaviour. Interestingly, μ receptor null mice show behavioural deficits similar to those observed in patients with autism spectrum disorder (ASD), including severe impairment in social interactions. Therefore, after a brief summary of recent evidence for blunted (social) reward processes in subjects with ASD, we review here arguments for altered μ receptor function in this pathology.

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Abbreviations

ACC, anterior cingulate cortex; ASD, autism spectrum disorder; CPu, caudate putamen; NAc, nucleus accumbens; PAG, periaqueductal gray; PFC, prefrontal cortex; SAS, social avoidance systems; USV, ultrasound vocalizations; VTA, ventral tegmental area

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Social reward and social pain: overlapping neurobiological substrates

Depending on internal state and environment, interactions with conspecifics in humans and animals may be experienced as aversive or pleasurable. Indeed, individuals may either compete for resources, territory, mates, social status or parental care (Roughgarden, 2012) when these are scarce or instead cooperate, play, mate, care for offspring, to ensure their survival and genetic legacy. In the latter case, social interactions can elicit pleasure and euphoria (Fehr and Camerer, 2007; Neuhaus *et al.*, 2010; Trezza *et al.*, 2010) and accordingly activate brain regions belonging to the reward processing circuitry. Social interaction or craving for social connection activates the nucleus accumbens (NAc) and medial prefrontal cortex (PFC) in humans (Fareri *et al.*, 2015; Kawamichi *et al.*, 2016; Inagaki *et al.*, 2016a). Conversely, activating reward regions such as ventral tegmental area (VTA) or dopaminergic raphe neurons in rodents promotes social interaction (Gunaydin *et al.*, 2014; Matthews *et al.*, 2016). Pleasure associated with social experience facilitates further social contact and may lead ultimately to the structuration of a social organization (Cacioppo *et al.*, 2011).

As a corollary of social organization, however, rejection by peers or loss of a close relative can be felt in social species as extremely painful, as much as an amputation (Parkes, 1975), and prolonged isolation elicits deleterious psychological and physical damages (Eisenberger *et al.*, 2016; Filipovic *et al.*, 2016). Remarkably, social rejection activates similar brain regions, such as the anterior cingulate cortex (ACC), anterior insula, periaqueductal gray (PAG) and amygdala, as physical pain (Kross *et al.*, 2011; Eisenberger, 2012; Hsu *et al.*, 2013; Papini *et al.*, 2015), suggesting that indeed rejected individuals experience 'social pain', which can be relived even more easily and more intensely than physical pain (Chen *et al.*, 2008). Importantly, social context, whether positive (such as images of loved ones in humans) or negative (rejection), can influence physical pain perception (Defeudis *et al.*, 1976; Puglisi-Allegra and Oliverio, 1983; Coudereau *et al.*, 1997; Younger *et al.*, 2010). Together, these data suggest that affiliative and social behaviours have hijacked primary reward and pain systems to promote social interactions and avoid adverse social contexts (Nelson and Panksepp, 1998).

At the neuronal level, many different neurotransmitters modulate social behaviour, either facilitating or inhibiting social interactions. Remarkably, most of the former are well-known key players of the reward system, such as **dopamine**, **noradrenaline**, cannabinoids, **oxytocin** or opioids (Dolen *et al.*, 2013; Coria-Avila *et al.*, 2014; Baribeau and Anagnostou, 2015; Loureiro *et al.*, 2016; Vanderschuren *et al.*, 2016), and have been initially identified as neurochemical mediators of the motivational/rewarding properties of drugs of abuse and/or as pain killers. In contrast, neurobiological substrates of social avoidance [social avoidance systems (SAS)] have been characterized as main factors of the pain, aggression or stress systems and include **5-HT**, glucocorticoids and neuropeptides such as **corticotropin-releasing factor**, **arginine vasopressin**, **substance P** or **cholecystokinin** (Katsouni *et al.*, 2009; Takahashi *et al.*, 2012; Barik *et al.*, 2013; Katsouni *et al.*, 2013; Gobbroge *et al.*, 2017). Pro-social and anti-social neuromodulators thus compete to drive adaptive social behaviour in individuals. In the following section, we will focus on the role of opioids and, more specifically, of the opioid **μ receptor**, in this subtle balance.

The μ receptor is a critical neurobiological substrate of social behaviour

The opioid receptors belong to the large family of GPCRs and include three members: μ, δ and κ opioid receptors, whose preferential endogenous ligands are the opioid peptides, **enkephalins**, **endorphins** and **dynorphins**, respectively. The opioid system is a well-known key modulator of pain, and exogenous ligands of opioid receptors, the opiates, have been used for thousands of years as pain killers. Medicinal use of opiates, however, has also led to the discovery of their addictive properties, shedding light on a second major physiological role of opioids: modulating reward processes. The identification of opioid peptides, their receptors and respective genes has since allowed a better understanding of their mechanism of action, regarding the control of pain and reward (Le Merrer *et al.*, 2009) as well as many other roles in stress response, respiration, food intake, gastrointestinal transit, endocrine and immune processes (Yamanaka and Sadikot, 2013; Sobczak *et al.*, 2014; Plein and Rittner, 2017).

In 1978, Panksepp and colleagues formulated their 'Brain Opioid Theory of Social Attachment' (BOTSA), in which social and affiliative behaviours are proposed to tightly depend on the level of endogenous opioid peptides, based notably on striking similarities between social attachment and drug addiction (Panksepp *et al.*, 1978). BOTSA hypothesizes that social deprivation induces social distress and contact seeking due to insufficient opioid tone (opioid withdrawal). Social contact would relieve this negative affect by triggering opioid (endorphin) release. Since then, experimental evidence has accumulated showing that μ receptors are primarily involved in pro-social effects of opioids, which are not only exclusively observed under social distress conditions (social deprivation or defeat) but also in more neutral or even positive social situations (social comfort). We review these data in the next subsections.

Role of μ receptors under social distress conditions

With regard to the role of μ receptors under social distress conditions (summary and references in Table 1 and Figure 1), the first evidence came from the observation that μ receptor agonists in infant rodents or monkeys can reduce the severe distress and ultrasound vocalizations (USV) triggered by separation from the mother. Similarly, in young adults, μ receptor agonists restore social interaction deficits and decrease defensive/submissive behaviour and USVs in isolated and defeated animals. Although social play is a highly rewarding and conserved behaviour in young social

Table 1

Effects of pharmacological manipulation of μ receptors on social behaviour

Species	Age	Housing	Drug	Dose	Route	Treatment schedule	Effects on social behaviour	References
Social distress								
Agonists								
Mouse	Young adults	Isolated 3 weeks	Morphine	+/++	Systemic	Acute	Decreased timid/defensive behaviour in females	Benton *et al.*, 1985
Rat	Pups	Isolated from mother	DAMGO	+	Intracisternal	Acute	Reduced USVs at all doses	Carden *et al.*, 1991
Rat	Juveniles	Isolated from weaning	Morphine	+	Systemic	Acute	Increased pinning in social play	Panksepp, 1979
Rat	Juveniles	Isolated from weaning	Morphine	+	Systemic	Acute	Increased social dominance slightly	Panksepp *et al.*, 1985
Rat	Juveniles	Isolated from weaning	Morphine	+	Systemic	Acute	Increased wanting to play	Normansell and Panksepp, 1990
Rat	Juveniles	Isolated from weaning	Morphine	+	Systemic	Chronic	Restored social exploration and contact	Van den Berg *et al.*, 1999
Rat	Juveniles	Isolated 3.5 h	Fentanyl	+	Systemic	Acute	Increased social play	Vanderschuren *et al.*, 1995b
Rat	Juveniles	Isolated 3.5 h	Morphine	+	Systemic	Acute	increased social play	Vanderschuren *et al.*, 1995a
Rat	Juveniles	Isolated 3.5 h	Morphine	+	Systemic	Acute	Increased social play in an unfamiliar environment	Trezza and Vanderschuren, 2008
Rat	Juveniles	Isolated 2 h	Morphine, DAMGO	+	NAc	Acute	Increased social play	Trezza *et al.*, 2011
Rat	Juveniles	Isolated 2 h	Beta-endorphin, Met-enkephalin	+	NAc	Acute	Increased social play	
Rat	Young adults	Isolated and defeated	DAMGO	+	VTA	Two times	Decreased defeat-induced inactivity	Nikulina *et al.*, 2005
Rat	Young adults	Isolated from weaning, defeated	Morphine	+/++	PAG ventrolateral	Acute	Decreased defeat-induced USVs	Vivian and Miczek, 1998
Macaque	Infants	Isolated from mother	Morphine	+	Systemic	Three times	Reduced USVs and isolation-induced inactivity	Kalin *et al.*, 1988
Macaque	Infants	Chronic separation with mother	Morphine	+	Systemic	Acute	Increased mother-infants clinging	Kalin *et al.*, 1995
Marmoset	Juveniles	Transparent physical separation	Morphine	+/−	Systemic	Acute	Increased social play	Guard *et al.*, 2002

(Continues)

Table 1 (Continued)

Species	Age	Housing	Drug	Dose	Route	Treatment schedule	Effects on social behaviour	References
Titi monkey	Young adults	30 min isolation	Morphine	+	Systemic	Acute	Increased affiliative behaviour in males and decreased female breaks Trend for reduced male approaches and reduced number of males initiating contact with pair-mate	Ragen *et al.*, 2015b
Antagonists								
Mouse	Young adults	Isolated from weaning	Naloxone	++	Systemic	Acute	Increased fearful/defensive postures when exposed to resident mouse	Brain *et al.*, 1985
Rat	Juveniles	Isolated 3.5 h	β-funaltrexamine	+	Systemic	Acute	Decreased social play	Vanderschuren *et al.*, 1995b
Rat	Juveniles	Isolated from weaning	Naloxone	+	Systemic	Acute	Decreased pinning in social play	Panksepp, 1979
Rat	Juveniles	Isolated from weaning	Naloxone	+	Systemic	Acute	Decreased wanting to play	Normansell and Panksepp, 1990
Rat	Juveniles	Isolated from weaning	Naloxone	+	Systemic	Acute	Decreased social dominance	Panksepp *et al.*, 1985
Rat	Juveniles	Isolated 8 days	CTAP	+	NAc	Acute	Decreased social play	Trezza *et al.*, 2011
Rat	Young adults	Isolated and defeated	Naloxone	+	Systemic	Acute	Increased defeat-induced chewing/teeth chattering and shakes	Chaijale *et al.*, 2013
Macaque	Infants	Isolated from mother	Naloxone	+	Systemic	Three times	Increased USVs	Kalin *et al.*, 1988
Macaque	Infants	Chronic separation with mother	Naltrexone	+	Systemic	Acute	Reduced mother-infants clinging	Kalin *et al.*, 1995
Titi monkey	Young adults	30 min isolation	Naloxone	+	Systemic	Acute	Increased female breaks	Ragen *et al.*, 2015b
Social comfort								
Agonists								
Rat	Young adults	Groups	Morphine	+	Systemic	Acute	Enhanced social recognition memory	Bianchi *et al.*, 2013
Rat	Young adults	Groups	Heroin	+/++	Systemic	Acute/ pretreatment	Enhanced social recognition memory	Levy *et al.*, 2009

(Continues)

Table 1 (Continued)

Species	Age	Housing	Drug	Dose	Route	Treatment schedule	Effects on social behaviour	References
Rat	Young males	Isolated with females	Endomorphin-1 Endomorphin-1	+ 	Medial POA Medial amygdala	Acute Acute	Increased mount and pursuit duration Increased mount number and ejaculation latency	Parra-Gamez *et al.*, 2013
Human	Young adults		Buprenorphine	+	Systemic	Acute	Increased ratings of images with social context Reduced attention to fear expressions and perceived social rejection	Bershad *et al.*, 2016
Human	Young adults		Buprenorphine	+	Systemic	Acute	Improved short term memory for happy expressions	Syal *et al.*, 2015
Human	Young men		Remifentanil	+	Systemic	Acute	Increased rating of pleasantness for neutral pictures	Gospic *et al.*, 2008
Human	Young men		Morphine	–	Systemic	3 days	Increased 'keep' presses for the most attractive female faces	Chelnokova *et al.*, 2014
Antagonists								
Mouse	Pups	Groups	Naltrexone	+	Systemic	First 4 days postnatal	Abolished preference for own cage and own mother in pups Abolished congener preference and social place preference in adults	Cinque *et al.*, 2012
Mouse KI Oprm1^{A112G}	Adults	Groups	Naloxone	+	Systemic	Acute	Abolished preference for congener in the three-chamber test	Briand *et al.*, 2015
Rat	Juveniles	Groups	CTAP	+	Lateral ventricule	Acute	Reduced social investigation time	Smith *et al.*, 2015
Prairie vole	Adult females	Isolated with males	Naltrexone	++	Systemic	Acute	Reduced mating bouts and suppressed partner preference	Burkett *et al.*, 2011
			Naltrexone	++	Systemic	Three times	Reversed preference for stranger versus partner	
			CTAP	++	NAc	Acute	No effect on partner preference	
			CTAP	++	CPu	Acute	Suppressed partner preference	
Prairie vole	Adult females	Isolated with males	CTAP	++	CPu	Acute	Suppressed partner preference and mating bouts	Resendez *et al.*, 2013
			CTAP	++	NAc core	Acute	No effect on partner preference and decreased mating bouts	

(Continues)

Table 1 (Continued)

Species	Age	Housing	Drug	Dose	Route	Treatment schedule	Effects on social behaviour	References
			CTAP	++	NAc dorsomedial shell	Acute	Suppressed partner preference and no effect on mating bouts	
			CTAP	++	NAc ventral shell	Acute	No effect on partner preference and mating bouts	
Macaque	Juveniles	Stable social group	Naloxone	+	Systemic	Acute	Increased proximity with mothers and demands for comfort	Schino and Troisi, 1992
Titi monkey	Young adults	Groups	Naloxone	+	Systemic	Acute	Reduced grooming and male approach	Ragen *et al.*, 2013
Titi monkey	Young adults	Groups	Naloxone	+	Systemic	Acute	Increased female breaks	Ragen *et al.*, 2015b
Human	Young adults		Naltrexone	+	Systemic	Acute	Increased negative emotions muscle responses to happy faces	Meier *et al.*, 2016
Human	Young adults		Naltrexone	+	Systemic	Four times	Reduced feeling of social connections	Inagaki *et al.*, 2016b
Human	Young adults		Naltrexone	+	Systemic	Four times	Decreased female face attractiveness	Chelnokova *et al.*, 2014
Excessive opioid stimulation								
Mouse	Young adults	Groups	Morphine	+++	Systemic	6 days, escalating	Reduced social interaction after 4 weeks of abstinence	Goeldner *et al.*, 2011
Mouse	Young adults	Groups	Heroin	+++	Systemic	6 days, escalating	Reduced social interaction after 4 and 7 weeks of abstinence	Lutz *et al.*, 2014
Mouse	Young adults	Isolated from weaning	Morphine	+++	Systemic	6 days, escalating	Reduced social interaction after 7 days of abstinence	Zanos *et al.*, 2014
Mouse	Young adults	Groups	Morphine	+++	Systemic	6 days, escalating	Reduced social interaction and social preference in three-chamber test after 4 weeks of abstinence	Becker *et al.*, in press
Rat	Young adults	Groups	Morphine	++/+++	Systemic	Acute	Decreased social recognition memory	Bianchi *et al.*, 2013
Rat	Young adults	Groups	Morphine	+	Systemic	Chronic	Reduced social exploration	Van den Berg *et al.*, 1999
Rat	Nullipares or lactating females	Isolated from weaning	Morphine	++	Dorsal POA	Acute	Decreased care for pups	Rubin and Bridges, 1984
Rat	Juveniles	Isolated 3.5 h	Morphine	++	Systemic	Acute	Decreased social play	Vanderschuren *et al.*, 1995a
Rat	Neonates	Females with their litters	Morphine	++	Systemic	23 days, escalating	Lag in development of social behaviours	Najam and Panksepp, 1989

(Continues)

Table 1 (Continued)

Species	Age	Housing	Drug	Dose	Route	Treatment schedule	Effects on social behaviour	References
Rat	Young adults	Females with their litters	Morphine	+++	Systemic	Chronic	Increased latencies for full maternal behaviour	Miranda-Paiva *et al.*, 2001
Rat	Young adults	Females with their litters	Morphine	++	Systemic	Chronic	Increased latencies for full maternal behaviour	Miranda-Paiva *et al.*, 2003
Rat	Young adults	Females with their litters	Morphine	+++	Systemic	Chronic	Disrupted maternal behaviour	Yim *et al.*, 2006
Prairie vole	Young adults	Isolated 1 week	Morphine	+++	Systemic	Acute	Reduced huddling duration	Shapiro *et al.*, 1989
Titi monkey	Young adults	Groups, with pair mates	Morphine	+	Systemic	Chronic, 7 days	Reduced grooming, tendency towards reduced contact	Ragen *et al.*, 2013

CTAP, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2; DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin, KI, knock-in; POA, preoptic area of hypothalamus.

mammals (Vanderschuren *et al.*, 2016), the common use is to isolate animals prior to its study, to increase social seeking (Table 1). In such mild negative social conditions, μ receptor agonists, delivered systemically, increase social play and motivation to play and reverse social dominance in juvenile rodents or monkeys. Furthermore, direct injection of μ receptor agonists in the NAc is sufficient to enhance social play, in accordance with the hedonic properties of μ receptor activation in this region. Besides, exposure to negative social contexts modifies brain μ receptor expression (Figure 1), notably in the NAc and VTA (Vanderschuren *et al.*, 1995c; Nikulina *et al.*, 2005; Chaijale *et al.*, 2013; Rodriguez-Arias *et al.*, 2016). In contrast with agonists, opioid antagonists exacerbate social distress and USV and increase the incidence of defensive postures. Together, therefore, pharmacological data in animals suggest that μ receptor activation can relieve distress in animals experiencing aversive social situations, whereas μ receptor blockade exacerbates such distress. In humans, imaging studies have revealed the activation of μ receptors under conditions of social rejection (notably in the NAc, amygdala and PAG) that correlated with lower levels of sadness and feeling of rejection, suggesting that μ receptors in these regions play a protective or adaptive role in social pain (Hsu *et al.*, 2013; Hsu *et al.*, 2015) (Figure 1). Whereas six other rare polymorphisms exist, the A118G polymorphism of the *OPRM1* gene (coding for the μ opioid receptor), removing a potential extracellular N-glycosylation site, is commonly found in European and Asian populations (15–60%) and considered as a gain-of-function *in vitro* and *in vivo* (Kroslak *et al.*, 2007; Sia *et al.*, 2008). A118G polymorphism carriers exhibit increased sensitivity to dramatic social rejection, leading to higher depression scores in adults (Way *et al.*, 2009; Hsu *et al.*, 2013; Slavich *et al.*, 2014; Carver *et al.*, 2016), more negative personality and impaired emotional, behavioural and social skills in children (Bertoletti *et al.*, 2012; Carver *et al.*, 2016). These last data suggest that μ receptor hyperactivity can be detrimental to coping with highly negative social experiences.

Role of μ receptors under neutral/positive social conditions

The role of μ receptor activation has also been extensively studied under conditions of social comfort (Table 1). In such context, low to moderate μ receptor activation facilitates social behaviour. In rats, μ receptor agonists increase socio-sexual and sexual behaviours, bias spatial exploration in an unfamiliar environment towards social play and enhance long-term social memory. In contrast, blockade of μ receptor activity inhibits various social behaviours when administered under neutral social context in animals, including social interaction, social play, affiliative and sexual or socio-sexual behaviours. The μ receptors in the NAc play a critical role in socio-sexual behaviour, as their expression in this structure is enriched in monogamous species (Inoue *et al.*, 2013; Ragen *et al.*, 2015a) and intra-NAc administration of antagonists abolishes partner preference formation (Table 1 and Figure 1). Remarkably, administering an opioid antagonist during the first four post-natal days in mice leads to social

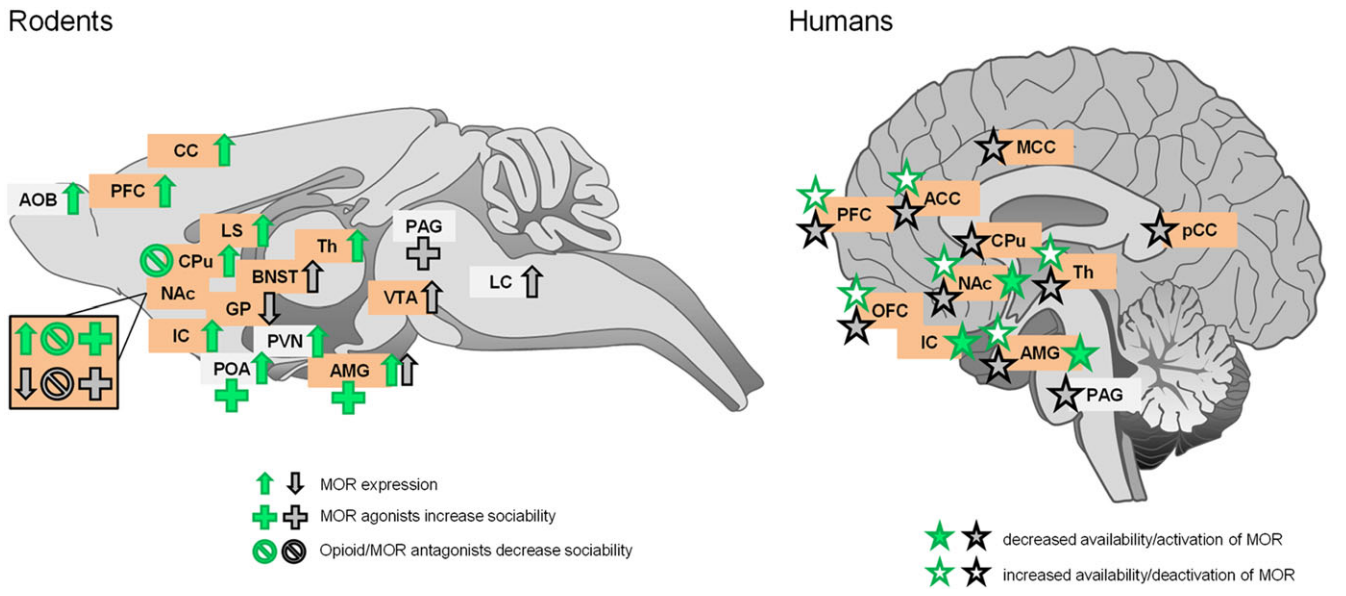

Figure 1

Effects of regional pharmacological manipulation of μ receptors (MOR) on social behaviour and regional μ receptor expression in rodents (left panel) and humans (right panel) under social comfort (green) or social distress (black) conditions. Lateralization of brain responses (right or left hemisphere) was not taken into account for simplification purpose. Pharmacological manipulations of μ receptors and modifications in μ receptor expression (in rodents) or availability (humans) affect similar brain regions, independently from the social context. These structures mostly belong to the reward circuitry (highlighted in orange). ACC, anterior cingulate cortex; AMG, amygdala; AOB, accessory olfactory bulb; BNST, bed nucleus of stria terminalis; CC, cingulate cortex; IC, insular cortex; GP, globus pallidus; LC, locus coeruleus; LS, lateral septum; MCC, middle cingulate cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; POA, preoptic area of hypothalamus; PVN, paraventricular nucleus of hypothalamus; Th, thalamus.

impairment and anhedonia in adult age. In humans, psychopharmacological studies have revealed that a low dose of μ receptor agonist increases female face attractiveness and avoidance of the least attractive female faces in men. Partial agonists improve memory for happy faces, increase pleasantness ratings of neutral or social images and decrease perception of social rejection (Table 1). Moreover, positive social stimuli such as social acceptance or pleasant social touch modify μ receptor availability in common structures (Hsu *et al.*, 2013; Nummenmaa *et al.*, 2016) (Figure 1). In contrast with agonists, opioid antagonists decrease facial emotional responses to happy faces, decrease female face attractiveness and reduce feelings of social connection in young adults. In humans, adult carriers of the A118G *OPRM1* polymorphism show less avoidance of affectionate relationships and increased capacity to experience social reward (Troisi *et al.*, 2011), whereas child carriers display improved relationships, better resilience to aversive parental care and enhanced responses to facial expression of social and emotional stimuli (Copeland *et al.*, 2011; Troisi *et al.*, 2011; Bertoletti *et al.*, 2012). Consistent with this, A118G *OPRM1* knock-in mice exhibit increased social interaction, dominance and protection from social defeat (Mague *et al.*, 2009; Briand *et al.*, 2015). Similarly, the C77G polymorphism in macaques, equivalent to the human A118G polymorphism, results in higher affiliative behaviour in mothers and infants (Barr *et al.*, 2008; Higham *et al.*, 2011). All these data thus converge to draw a pro-social picture for μ receptors under neutral/positive social conditions.

The particular case of excessive and/or prolonged opioid stimulation

Surprisingly, however, several studies have reported that μ receptor agonists administered either acutely at a moderate to high dose or chronically at a low dose inhibit various social behaviours such as socio-sexual behaviours, maternal behaviour and duration of direct social exploration independently from the social context (Table 1). Interestingly, in the clinics, former opiate addicts under opioid maintenance (chronic low dose) display social interaction/cognition deficits, report feeling of being unrelated and behave in an autistic way (McDonald *et al.*, 2013; Johnson *et al.*, 2014). In other studies, high doses of a μ receptor agonist, given acutely or chronically, reduce socio-sexual behaviour, social play and impair long-term social memory in animals. Furthermore, exposure to high doses of opiates affects social behaviour in the long term, as mice exposed to escalating doses of morphine or heroin display severe social interaction deficit up to 7 weeks after cessation of treatment (Table 1). Of note, brain transcription of opioid peptides is reduced after 4 weeks in abstinent animals (Becker *et al.*, in press) suggesting that excessive opioid stimulation results in long lasting adaptive peptide down-regulation. Accordingly, opiate-abstinent patients without substitutive therapy show low levels of circulating β-endorphin (Shi *et al.*, 2009) and display reduced prefrontal response to social stimuli, pointing to social behaviour deficits (Huhn *et al.*, 2016). Together, these data indicate that, when excessive and/or prolonged, μ

receptor activation can exert a deleterious influence on social behaviour.

The μ receptor balance model

In an attempt to solve the paradox of divergent effects of μ receptor stimulation on social behaviours depending on species (rodents vs. primates/humans), a 'State-dependent μ-Opioid Modulation of Social Motivation' (SOMSOM) model was recently proposed. This model postulates that the effects of μ receptor agonists and antagonists depend on the social motivational state of the animals when assessing their behaviour, namely, whether they are trying to reduce distress or seeking a pleasurable experience (Loseth *et al.*, 2014). In this model, the initial social context is the crucial determinant of future effects of opioid manipulation on sociability. However, although this model successfully predicts the consequences of μ receptor stimulation and inhibition under social distress or comfort conditions, it fails to account for negative consequences of intense and/or long-lasting μ receptor stimulation. Extending the SOMSOM model, we propose a μ receptor balance model (Figure 2), in which the key determinant to predict the consequences of opioid/μ receptor manipulation on social behaviour is the initial μ receptor activity. In this model, both excessive and deficient μ receptor activity negatively influence social behaviour through a classical inverted-U relationship (Johnson *et al.*, 2014). In a narrow window of optimal functioning, μ receptor activity could be balanced with SAS to allow adaptive social behaviour. In contrast, blunted μ receptor activity, due to social distress or pharmacological antagonism, leads to reduced social reward/motivation and leaves the field clear for SAS to elicit social withdrawal. Similarly, excessive μ receptor stimulation due to intense/prolonged exposure to opioids saturates the reward system and produces social indifference. In this framework, blocking μ receptor activity in the case of excessive tone, or stimulating μ receptor when the tone is too low, can restore normal, adaptive, social behaviour. The μ receptor balance model thus reconciles experimental discrepancies regarding the social consequences of μ receptor stimulation depending on species and social context.

Manipulation of μ receptors in different social contexts might face some technical issues of other non-specific functions of the μ receptor (locomotion and sedation) affecting social behaviour. However, our conclusions are drawn on studies involving different doses of μ receptor ligands and studying different kind of social behaviours and also non-social behaviours, excluding issues regarding

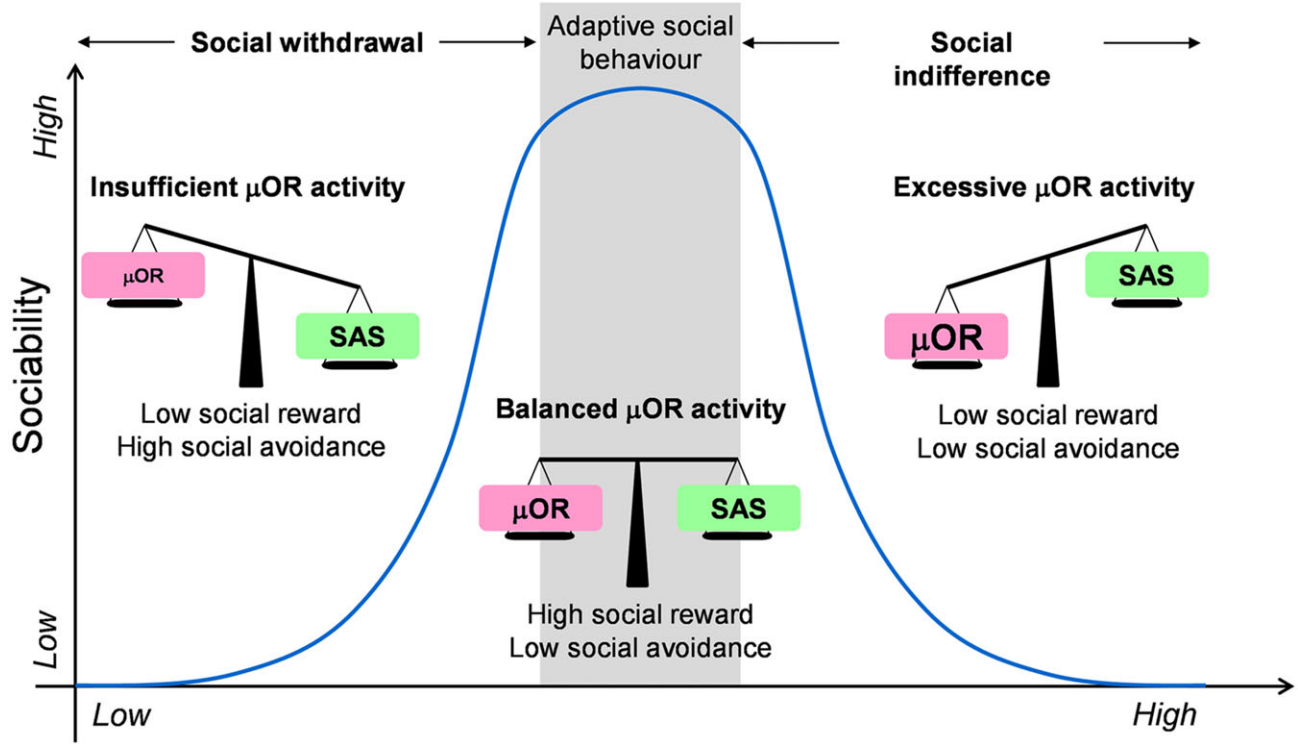

Figure 2

The μ receptor balance model. Activity of μ receptors (μOR) competes with SAS to drive social behaviours. In a narrow window of optimal functioning, μ receptor activity is balanced with SAS to allow adaptive social behaviour. These conditions are ideal to detect social reward (good signal to noise ratio). On the left part of the curve, low μ receptor activity, due to social distress, pharmacological antagonism or genetic anomaly, leads to reduced social reward and/or motivation and leaves the field clear for SAS to elicit social withdrawal (insufficient signal). On the right part of the curve, excessive μ receptor activity, due to intense and/or prolonged exposure to opioid ligands or increased μ receptor expression, saturates the reward system and produces social indifference (excessive noise). Importantly, in this model, blocking μ receptor activity in the case of excessive tone, or stimulating μ receptor when the tone is too low, can restore normal, adaptive, social behaviour.

other μ receptor functions and their effects on social behaviours.

Genetic manipulations of the μ opioid receptor and autistic-like syndrome in mice

Genetic knockout of μ receptors (*Oprm1*$^{-/-}$) produces severe alterations of social behaviour in mice. Indeed, mouse pups lacking μ receptors vocalize less when separated from their mother (Moles *et al.*, 2004; Cinque *et al.*, 2012), juvenile *Oprm1*$^{-/-}$ mice exhibit reduced interest in social partners (Cinque *et al.*, 2012), young adult *Oprm1*$^{-/-}$ males respond less to female vocalizations (Wohr *et al.*, 2011; Gigliucci *et al.*, 2014) and *Oprm1*$^{-/-}$ male and female animals display reduced social interaction and preference (Becker *et al.*, 2014). However, when exposed to chronic social defeat, μ receptor knockout animals show less aversion to the social context (Komatsu *et al.*, 2011). These data fit with the μ receptor balance model (insufficient μ receptor tone) and further demonstrate that μ receptors are essential for establishing appropriate social behaviour.

Interestingly, *Oprm1*$^{-/-}$ mice were recently proposed as a monogenic mouse model of autism spectrum disorder (ASD) (Oddi *et al.*, 2013; Becker *et al.*, 2014). ASD are complex neurodevelopmental diseases whose diagnosis is based on the detection of two types of behavioural symptoms (core symptoms): impaired social reciprocity and communication together with restricted, repetitive patterns of behaviour, interests or activities (Diagnostic and Statistical Manual of Mental Disorders: DSM-5). Co-morbid symptoms, variable in their occurrence and intensity, are frequently associated with ASD and encompass anxiety disorders, cognitive and motor deficits, aggressive behaviour, epileptic episodes, sleep disturbances, increased sensitivity to pain and altered gastrointestinal transit (Johnson and Myers, 2007; Robinson, 2012; Veenstra-VanderWeele and Blakely, 2012; White *et al.*, 2012; Mazurek *et al.*, 2013; Whyatt and Craig, 2013; Chen *et al.*, 2016). Intriguingly, in addition to deficits in social behaviour, *Oprm1*$^{-/-}$ mice show stereotyped and perseverative behaviours, necessary to fulfil ASD criteria, as well as many of the co-morbid symptoms of ASD, namely, increased aggressiveness, exacerbated anxiety and motor clumsiness (Becker *et al.*, 2014), increased susceptibility to seizures (Jang *et al.*, 2001; Grecksch *et al.*, 2004; Becker *et al.*, 2014), impaired spatial learning (Jamot *et al.*, 2003), lowered nociceptive thresholds (Gaveriaux-Ruff and Kieffer, 2002) and reduced gastrointestinal motility (Roy *et al.*, 1998). The μ receptor null mice thus reproduce the broadest autistic syndrome ever reported in preclinical research, proving unique face validity. Moreover, *Oprm1*$^{-/-}$ mice display anatomical, neurochemical and genetic landmarks of the disease, such as modified neuronal activation in anxiety- and reward-associated brain structures, reduced striatal connectivity, altered synaptic morphology and monoamine levels in the striatum and modified expression of several candidate genes of autism, providing construct validity to the model (Becker *et al.*, 2014; Mechling *et al.*, 2016). Finally, as regards predictive validity, risperidone and oxytocin, compounds that demonstrated efficiency in relieving autistic features in patients, also alleviated such symptoms in μ receptor null mice (Becker *et al.*, 2014; Gigliucci *et al.*, 2014). Together, these results establish the *Oprm1*$^{-/-}$ mouse line as a comprehensive model of ASD and demonstrate that genetic invalidation of μ receptors is sufficient to trigger an autistic syndrome in these rodents.

Preclinical studies exploring *MECP2*-related genetic diseases further support the hypothesis of a tight link between ASD and μ receptors. The *MECP2* gene codes for methyl-CpG binding protein 2, which binds DNA at methylated sites to either repress or activate transcription (Chahrour *et al.*, 2008). Genetic invalidation of *Mecp2* in mice is a model for Rett syndrome, which includes autistic features; conversely, *Mecp2* duplication mimics the *MECP2* duplication syndrome, which also encompasses autistic symptoms (Lombardi *et al.*, 2015). Remarkably, μ receptor expression is decreased in the striatum of *Mecp2* null mice (Kao *et al.*, 2015), consistent with a critical role of μ receptors in the striatum in supporting social behaviour. In mice bearing multiple copies of *Mecp2*, however, μ receptor expression is instead excessive, and breeding these animals with heterozygous *Oprm1*$^{+/-}$ mice corrects both high μ receptor expression and deficient social interaction (Samaco *et al.*, 2012). These data fit the μ receptor balance model, with both deficient and excessive signalling having deleterious consequences (Figure 2). Most importantly, they further establish a connection between μ receptor and ASD, suggesting that defective μ receptor function could account for decreased social reward/motivation in these disorders.

Evidence for blunted reward processes in autism spectrum disorder

In search of the neurobiological underpinnings of disrupted social interactions in ASD, autism research had initially focused on cognitive impairments and involved theory-of-mind deficits or altered ability to infer other's mental states. Recently, however, motivational aspects of social skills have received more attention, and a social motivation theory has emerged (Dawson and Bernier, 2007; Chevallier *et al.*, 2012). In this framework, disrupted social interest in ASD patients would result from early deficits in social motivation, including interest in attending social stimuli, as well as enjoying and prolonging reciprocal social interactions. Such interactions being intrinsically rewarding (Fehr and Camerer, 2007; Neuhaus *et al.*, 2010; Trezza *et al.*, 2010), the social motivation theory thus suggests that reward and/or social reward processes are altered in patients with ASD.

Consistent with this hypothesis, numerous psychological studies have shown diminished sensitivity to the positive reward value of social stimuli in subjects with ASD (Scott-Van Zeeland *et al.*, 2010; Chevallier *et al.*, 2012; Lin *et al.*, 2012; Sasson *et al.*, 2012; Dubey *et al.*, 2015; Kim *et al.*, 2015). Accordingly, electrophysiological (Stavropoulos and Carver, 2014; Gonzalez-Gadea *et al.*, 2016) and pupillary (Sepeta *et al.*, 2012) responses as well as neural activation in brain areas involved in reward anticipation and/or processing (notably PFC and NAc) (Scott-Van Zeeland *et al.*, 2010; Kohls *et al.*, 2012; Assaf *et al.*, 2013; Kohls *et al.*, 2014; Richey *et al.*,

2014; Choi *et al.*, 2015; Leung *et al.*, 2015) are diminished in ASD patients presented with social stimuli (Figure 3). Of note, subjects with ASD also display hypo-activated NAc and caudate putamen (CPu) while anticipating negative social reinforcement (Damiano *et al.*, 2015) and diminished activity in the social brain circuitry (including PFC and amygdala) in response to social touch (Kaiser *et al.*, 2016). As regards the amygdala and insular cortex, also involved in reward processing, studies have reported either hypo-activation (Kohls *et al.*, 2012; Leung *et al.*, 2015; Kaiser *et al.*, 2016) or hyper-activation (Dichter *et al.*, 2012b) in response to social stimuli in ASD subjects, possibly due to different experimental settings. Together, these data strongly support the hypothesis of deficient social reward in patients with ASD, as a likely consequence of abnormal activation of the brain reward circuit in social contexts.

Clinical data relative to other (non-social) rewarding stimuli appear less consistent. Concerning primary rewards, individuals with ASD were reported to display intact hedonic responses to sweet taste (Damiano *et al.*, 2014) and stronger activation in brain reward regions (NAc, orbitofrontal cortex, amygdala and insula) in response to food cues (Cascio *et al.*, 2012a) pointing to increased food reward in these patients. In line with this, children with ASD were shown as less able to delay gratification when tested for a food reward (Faja and Dawson, 2015). In contrast, ASD subjects exhibited diminished brain activation for pleasant (and neutral) tactile texture stimuli (Cascio *et al.*, 2012b) and young children with ASD were impaired in learning an abstract rule from a discrete physical reward (small toy) (Jones *et al.*, 2013). Consistent with this, when presented with an object incentive, adults with ASD showed decreased activation in the dorsal ACC but increased activation in the paracingulate gyrus and other frontal regions (Dichter *et al.*, 2012a). These data suggest that reward processing for these stimuli is altered in ASD patients. Regarding secondary rewards, some studies have reported unchanged anticipation and processing of monetary reward (Dvash *et al.*, 2014) and no modification of neural responses during monetary choices (Gonzalez-Gadea *et al.*, 2016) in patients with ASD. In other reports, these patients were shown to be less sensitive to monetary incentive (Scott-Van Zeeland *et al.*, 2010; Lin *et al.*, 2012; Kohls *et al.*, 2014), notably when making effort-based decisions (Damiano *et al.*, 2012), and more sensitive to monetary loss (South *et al.*, 2014). Accordingly, imaging studies have disclosed hypo-activation in the mesocorticolimbic circuitry (NAc,

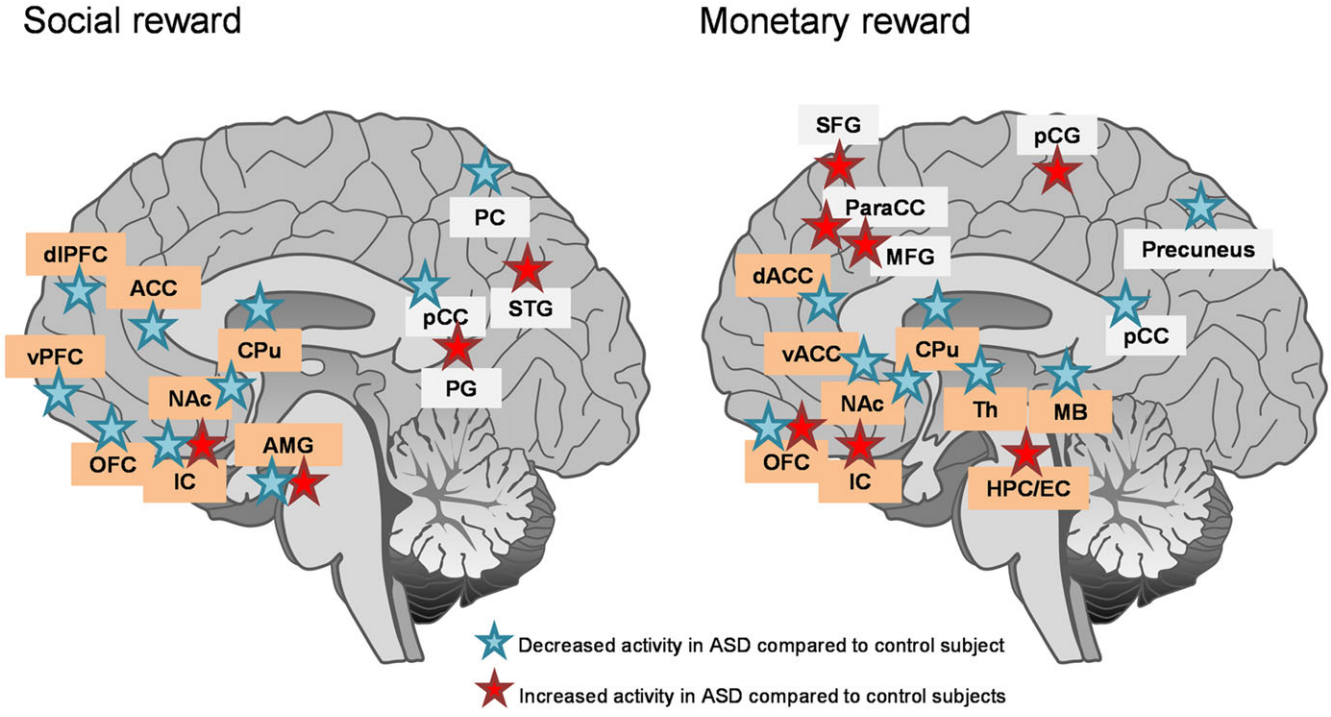

Figure 3

Brain areas differentially activated in patients with ASD versus controls during social (left panel) or monetary (right panel) reward anticipation and/or processing. Lateralization of brain responses (right or left hemisphere) was not taken into account to simplify the proposal. Comparing brain activation patterns for social and monetary reward reveals a common hypoactivation of a frontostriatal circuit including key regions for reward processing that are ACC, NAc and CPu in patients with ASD. The nature of stimuli used for experiments (images of faces, verbal praise and social reinforcement), tasks performed (stimulus presentation vs game or learning task for example) and timing (anticipation vs reward processing) varied across studies, possibly accounting for discrepancies in the level of activation of some structures (IC, AMG and OFC). Brain regions belonging to the reward circuitry are highlighted in orange. ACC, anterior cingulate cortex; AMG, amygdala; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; HPC/EC, hippocampus/enthorinal cortex; IC, insular cortex; MB, midbrain; MFG, medial frontal gyrus; OFC, orbitofrontal cortex; paraCC, paracingulate cortex; PC, parietal cortex; pCC, posterior cingulate cortex; PCG, precentral gyrus; PG, parahippocampal gyrus; SFG, superior frontal gyrus; STG, superior temporal gyrus; vPFC, ventral prefrontal cortex.

Table 2

Levels of blood, CSF or urinary opioid peptides in subjects with ASD or Rett Syndrome

Opioid peptide	Fluid	Detection method	Number of subjects	Results	References
β-Endorphin	Plasma	RIA	13	Similar in ASD and controls	Ernst *et al.*, 1993
β-Endorphin	Plasma	RIA	10	Decreased in ASD compared to controls	Weizman *et al.*, 1984
β-Endorphin	Plasma	RIA	22	Decreased in ASD compared to controls	Weizman *et al.*, 1988
β-Endorphin	Plasma	RIA	67	Increased in ASD compared to controls	Leboyer *et al.*, 1994
			22	Increased in Rett Syndrome compared to controls	
β-Endorphin	Plasma	RIA	62	Increased in mothers of children with ASD compared to controls	Leboyer *et al.*, 1999
β-Endorphin	Plasma	RIA	10	Increased in ASD compared to controls	Bouvard *et al.*, 1995
β-Endorphin	Plasma	RIA	33	Increased in ASD compared to controls	Willemsen-Swinkels *et al.*, 1996
β-Endorphin	Plasma	RIA	48	Increased in ASD compared to controls	Tordjman *et al.*, 1997
β-Endorphin	Plasma	RIA	12	Increased in ASD compared to controls	Brambilla *et al.*, 1997
β-Endorphin	Plasma	RIA	11	Increased in ASD compared to controls	Cazzullo *et al.*, 1999
β-Endorphin	Plasma	RIA	73	Increased in ASD compared to controls	Tordjman *et al.*, 2009
β-Endorphin	CSF	RIA	19	Similar in ASD and controls	Nagamitsu, 1993
β-Endorphin			3	Increased in Rett Syndrome compared to controls	
β-Endorphin	CSF	RIA	22	Similar in ASD and controls	Nagamitsu *et al.*, 1997
β-Endorphin	CSF	RIA	9	Decreased in Rett Syndrome compared to controls	Genazzani *et al.*, 1989
β-Endorphin	CSF	RIA	31	Decreased in ASD compared to controls	Gillberg *et al.*, 1990
β-Endorphin			8	Decreased in Rett Syndrome compared to controls	
β-Endorphin	CSF	RIA	9	Increased in ASD compared to controls	Ross *et al.*, 1987
Met-Enkephalin	CSF	RIA	24	Increased in ASD compared to controls	Gillberg *et al.*, 1985
Opioid Peptides	Urine	HPLC	54	Not detected	Dettmer *et al.*, 2007
Opioid Peptides	Urine	Mass Spec	10	Not detected	Shattock *et al.*, 2004
Opioid Peptides	Urine	HPLC	97	Not detected	Pusponegoro *et al.*, 2015
Opioid Peptides	Urine	Mass Spec	65	Similar in ASD and controls	Cass *et al.*, 2008
β-Casomorphin	Urine	ELISA	10	Increased in ASD compared to controls	Sokolov *et al.*, 2014
β-Casomorphin	Urine	HPLC	53	Increased in Rett Syndrome compared to controls	Solaas *et al.*, 2002
			35	Increased in ASD compared to controls	
Exorphins	Urine	HPLC	135	Increased in ASD compared to controls	Reichelt *et al.*, 2012

Mass Spec, mass spectrometry.

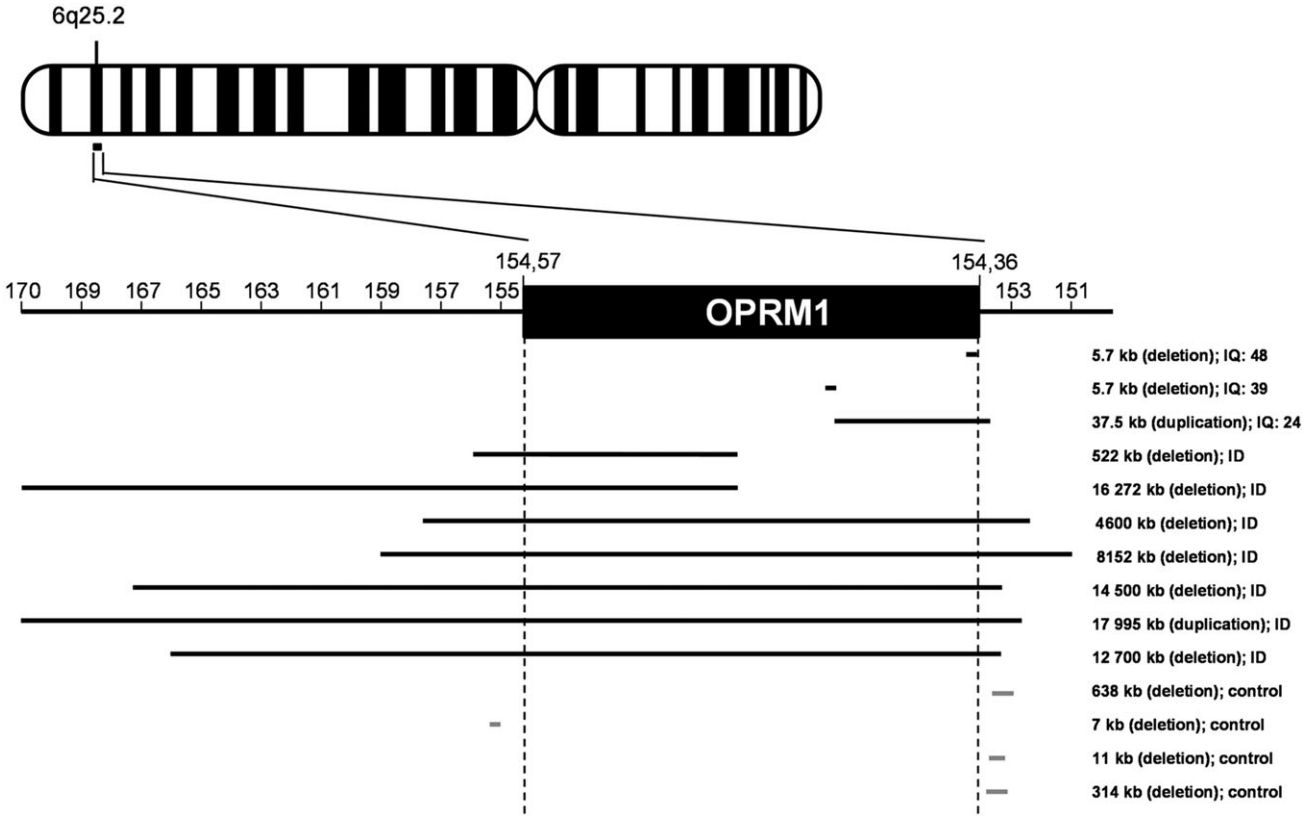

Figure 4

Copy number variation in the *OPRM1* gene of patients with ASD. *OPRM1* is located on chromosome 6 at the q25.2 position. The map was build based on the integrated catalogue of copy number variants (CNVs) associated with ASD from the Simons Foundation Autism Research Initiative resource website (https://gene.sfari.org/autdb/CNVHome.do; September 2016). We identified 10 patients from this database displaying CNVs that affect the *OPRM1* gene (eight deletions and two duplications) (Kaminsky *et al.*, 2011; Sanders *et al.*, 2011; Halgren *et al.*, 2012; Battaglia *et al.*, 2013). No CNVs were detected in controls, some of which showed mutations immediately beyond *OPRM1* boundaries. Remarkably, *OPRM1* CNVs were all detected in low-functioning ASD subjects (with intellectual disability). ID, intellectual deficiency; IQ, intellectual quotient.

CPu and midbrain) during monetary anticipation or outcome in ASD patients (Kohls *et al.*, 2012; Dichter *et al.*, 2012a; Dichter *et al.*, 2012b; Richey *et al.*, 2014) (Figure 3). Moreover, children with ASD were found to display reduced activation of the right CPu when anticipating monetary loss (Damiano *et al.*, 2015). Finally, when reward stimulus was a positive feedback ('Correct!' printed on screen) versus negative feedback ('incorrect!'), young adults with ASD displayed impaired ability to develop an effective reward-based working memory (Solomon *et al.*, 2015). These data converge towards altered processing of secondary reward in ASD patients. However, ASD subjects can attribute higher positive ratings to non-social stimuli whenever these stimuli match their restricted interests (trains and electronics) (Sasson *et al.*, 2012; Watson *et al.*, 2015). Non-social reward processes thus appear unevenly affected by ASD, with food reward and restricted interests showing increased motivational value, whereas other stimuli show blunted motivational properties.

Methodological issues should be mentioned, though, that may limit previous conclusions. Indeed, a major difficulty in clinical ASD research lies in recruiting patients. Notably, sample size in a majority of studies is small and the age of participants is highly heterogeneous (young children, adolescents and adults) as well as patient's use of psychotropic medications or involvement in behavioural therapy programs, which has significant consequences on reward processing (Pankert *et al.*, 2014). Most importantly, clinical studies suffer from a major IQ bias: They focus on a population of subjects with IQ in a normal range, namely, higher functioning ASD patients. This bias is essentially due to technical issues, as most psychological tasks and imaging settings in previous studies are too demanding and restrictive for lower functioning subjects. The possibility that the latter patients present more severe reward deficits has thus never been explored. Of importance though, conditioned learning mechanisms are set very early in the course of human infant development (Rovee-Collier, 1999) and depend tightly, as regards appetitive aspects, on the integrity of the reward system (Dayan and Balleine, 2002; O'Doherty *et al.*, 2016). Major deficits in reward processing may thus result in cognitive impairment, such as observed in low functioning ASD patients, highlighting the interest of evaluating reward in this population.

In conclusion, clinical data have demonstrated deficient reward processing in patients with ASD, for social and secondary (monetary) stimuli. The neurobiological substrates

of this deficit remain to be identified, and one possible candidate is a dysfunction of the opioid system.

The opioid hypothesis in autism

As a straightforward consequence of BOTSA (Panksepp *et al.*, 1978), Panksepp proposed for the first time in 1979 that autism would be an emotional disorder caused by excessive brain opioid activity and, therefore, that opioid antagonists should be beneficial to treat this pathology (Panksepp, 1979). The last hypothesis was later tested by administering **naltrexone** to ASD patients. Several clinical trials showed beneficial effects of naltrexone in reducing hyperactivity and irritability, but failed to detect an improvement in core autistic symptoms (reviewed in (Roy *et al.*, 2015)), except maybe in a subgroup of patients with high blood levels of β-endorphins (Leboyer *et al.*, 1992; Bouvard *et al.*, 1995). Consistent with the excessive opioid hypothesis, several studies have reported increased (but also decreased) levels of opioid peptides in plasma, urinary and cerebrospinal fluid samples from patients with ASD (Table 2). Reichelt and colleagues proposed a dietary origin for urine peptides (Reichelt *et al.*, 1991) and therefore recommended a gluten- and casein-free diet to relieve ASD (Knivsberg *et al.*, 1999). Technical issues were raised, however, regarding the concentrations of urinary opioid peptides that challenged Reichelt's hypothesis and led to a still active scientific controversy. In further questioning of the excessive opioid theory, reviews and meta-analyses have examined clinical evidence for the efficacy of dietary intervention in autism and found a lack of consistent effects (Dosman *et al.*, 2013; Mari-Bauset *et al.*, 2014; Lange *et al.*, 2015). In sum, technical concerns and disappointing clinical results have argued against the excessive opioid theory of autism and, more generally, dissuaded the scientific community from considering dysfunction in the opioid system as a plausible neurobiological substrate for autism.

The hypothesis of excessive opioid activity in autism fits into the excessive opioid tone window of our μ receptor balance model (Figure 2). However, this model also predicts that ASD could result from insufficient opioid tone. Interestingly, there is clinical evidence supporting both propositions. Dosage studies have examined levels of opioid peptides in various biological samples from patients with autism. As regards plasma samples, most studies have detected an increase in circulating β-endorphin in subjects with ASD (or their mothers) or Rett syndrome (Table 2). Whether such increase would reflect an excessive opioid tone in these patients or, instead, reflects a compensation for defective opioid signalling, as suggested by abnormal β-endorphin immunoreactivity (Leboyer *et al.*, 1994) or decreased μ receptor expression in a mouse model of Rett syndrome (Kao *et al.*, 2015), has not been explored yet. Of note however, low doses of naltrexone, known to stimulate μ receptor expression (Brown and Panksepp, 2009), significantly relieved autistic symptoms in several ASD patients (Leboyer *et al.*, 1992; Bouvard *et al.*, 1995). Regarding cerebrospinal fluid and urine samples, levels of β-endorphin or, more generally, opioid peptides appear inconsistent, possibly due to methodological issues. Urinary exogenous (presumably dietary) opioid peptides have been detected in several studies (Table 2). Together, these data argue for a link between opioid tone and ASD, in either direction (excessive or deficient tone). Genetic studies further support the existence of such connection. We browsed the SFARIgene[2.0] database (https://gene.sfari.org/autdb/Welcome.do) in search for mutations affecting opioid genes in ASD patients. We failed to find mutations in genes coding for the precursors of endorphins (*POMC*) or dynorphins (*PDYN*) and for δ or κ receptors (*OPRD1*, *OPRK1*). We found one patient with a genetic deletion including *PENK*, coding for proenkephalin (Kaminsky *et al.*, 2011). Strikingly, however, we found 10 patients with mutations affecting the *OPRM1* gene (Figure 4). For comparison, mutations in *CNR1*, coding for the **CB_1 cannabinoid receptor**, another candidate gene for ASD involved in reward processing (Chakrabarti *et al.*, 2006), are not reported in the SFARIgene[2.0] database. In addition, *OPRM1* mutations are all associated with intellectual deficiency, suggesting that compromised μ receptor function in humans can lead to IQ impairment. Genetic data thus demonstrate that genetic μ receptor ablation is sufficient to produce ASD in humans, as it is in mice (Becker *et al.*, 2014). Direct genetic mutation, though, is not the only way to impair the expression and function of a GPCR, as illustrated by the effects of *Mecp2* genetic manipulation on μ receptor expression in mice. Whether mutations in other candidate genes for autism identified from sequencing studies could affect μ receptor signalling thus needs to be carefully explored.

Conclusions

Recent advances in brain imaging and sustained efforts towards identifying the genetic and neurobiological substrates of social impairment in ASD, including characterization of mouse models, have revived the exciting field of opioids and social behaviour. These studies have provided the demonstration that, among factors of the opioid system, μ receptors are the key substrate for the control of social behaviour. In an attempt to better describe the role of μ receptors in such control, we propose here a new model, the μ receptor balance model, in which both deficient and excessive μ receptor signalling results in social behaviour impairments. How this model could apply to other opioid-dependent functions would need further investigation. Importantly, altered μ receptor function is clearly *sufficient* to hamper social abilities, making it a plausible contributor to ASD. Dedicated studies are now required to explore the *necessity* of μ receptor dysfunction for social impairment in such pathologies. Remarkably, pharmacological treatments can relieve autistic-like symptoms in μ receptor null mice (Becker *et al.*, 2014; Gigliucci *et al.*, 2014), suggesting that whether or not μ receptor dysfunction is a core mechanism in ASD, promising therapeutic strategies exist that can overcome such dysfunction.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org,

the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015).

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Conflict of interest

The authors declare no conflicts of interest.

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